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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,132	06/20/2003	Anthony P. Shuber	EXCT-31012/US-1/PRI	4962

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Casimir Jones, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562

EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.**	**Applicant(s)**
	10/601,132	SHUBER, ANTHONY P.
	Examiner	**Art Unit**
	SEAN AEDER	1642

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 12 October 2011 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,4-8,11,14,19-21,24,28-30 and 35-40*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

13. ☐ Other: _____.

/Sean E Aeder/
Primary Examiner, Art Unit 1642

Continuation of 11. does NOT place the application in condition for allowance because: Claims 1, 4-8, 11, 14, 19-21, 24, 28-30, and 35-40 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Lapidus et al (US 6,143,529; 11/7/00) in view of Hromadnikova et al (BMC Pregnancy and Childbirth, 5/28/02, 2(4):1-5) for the reasons stated in the Office Action of 8/12/11 and for the reasons set-forth below.

Lapidus et al teaches a method for identifying a patient as a candidate for additional colorectal cancer testing comprising the steps of: determining a quantitative amount of patient genomic DNA in a stool sample comprising shed cells and shed cellular debris, wherein the quantitative amount is determined by using quantitative PCR to measure an amount of nucleic acid fragments amplified from heterologous DNA that has not been specifically isolated from other DNA of a supernant from a centrifuged stool sample comprising DNA from shed cells and shed cell debris, wherein a higher amount of "amplifiable genomic DNA" (as clearly illustrated in Figure 1, "amplifiable DNA" includes amplification products less than 200 bp) and/or amplifiable genomic DNA in a stool sample "greater than about 200 bp", as compared to a healthy individual, is indicative of a need for further screening and predictive of colorectal cancer because patients with adenoma in the colon slough more cells than healthy individuals (see lines 44-55 of column 4, lines 36-44 of column 5, lines 47-56 of column 7, and claims 1, 6, and 7, in particular). Lapidus' methods of detecting "amplifiable DNA" and/or DNA "greater than about 200 bp" includes methods that amplify fragments of 200 bp. Such a teaching by Lapidus et al is FULLY in line with what is disclosed in the instant specification: amplified fragments 200 bp or greater are indicative of cancer, while fragments less than 200 bp are indicative of apoptosis (see [039] of the instant specification, in particular). Lapidus et al further teaches that patients identified as possibly having colon cancer by one method would also be subjected to other methods of testing for colon cancer (lines 8-10 of column 4, in particular). Such other methods comprise performing other diagnostic methods on the stool sample, LOH assay, detection of ras mutation, and colonoscopy (column 4, in particular).

Lapidus et al does not specifically describe the amounts of genomic DNA as "genome equivalents". However, this deficiency is made up in the teachings of Hromadnikova et al.

Hromadnikova et al teaches a quantitative PCR method of comparing amounts of DNA between samples comprising expressing amounts of DNA in terms of "genome equivalents" (page 2 right column, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to perform the methods of Lapidus et al by describing the amounts of amplifiable DNA and DNA greater than about 200 bp in terms of genomic equivalents because describing amounts of DNA in terms of genomic equivalents effectively normalizes data between multiple samples and assays. Further, one would have been motivated to perform said methods by detecting 200 bp fragments because Lapidus et al teaches a high amount of amplifiable genomic DNA greater than about 200 bp in a stool sample, as compared to a healthy individual, is indicative of a need for further screening and predictive of colorectal cancer because patients with adenoma in the colon slough more cells than healthy individuals. Further,one would have been motivated to perform said methods by detecting fragments less than 200 bp because Lapidus et al teaches a high amount of amplifiable genomic DNA (which includes amplified fragments less than 200 bp; see Figure 1), as compared to a healthy individual, is indicative of a need for further screening of colorectal cancer because patients with adenoma in the colon slough more cells than healthy individuals. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for performing the methods of Lapidus et al by describing amounts of DNA in terms of genomic equivalents and detecting amplified DNA having lengths of 200bp because Hromadnikova et al teaches how to determine genome equivalents and because Lapidus et al teaches a high amount of amplifiable genomic DNA in a stool sample, as compared to a healthy individual, is indicative of colorectal cancer because patients with adenoma in the colon slough more cells than healthy individuals. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

In the Reply of 10/12/11, Applicant argues that the cited references do not teach amplification directly from heterogeneous DNA comprising human DNA that has not been specifically isolated from other DNA in supernant because Lapidus teaches human DNA to be amplified is purified by sequence-specific capture prior to amplification. Applicant further indicates that Lapidus' teaching of "greather than about 200 bp" does not include 200 bp. Applicant further argues that the cited references do not teach quantifying patient DNA in a stool sample by measuring an amount of nucleic acid fragments amplified from heterogenous DNA isolated from supernant from a centrifuged sample comprising stool sample and buffer, wherein said heterogeneous DNA comprises human DNA that has not been specifically isolated from other DNA in the supernant. Applicant further argues that motivation for combining the cited references has not been provided.

The arguments found in the Reply of 10/12/11 have been carefully considered, but are not deemed persuasive. In regards to the argument that the cited references do not teach amplification directly from heterogeneous DNA comprising human DNA that has not been specifically isolated from other DNA in supernant because Lapidus teaches human DNA to be amplified is purified by sequence-specific capture prior to amplification, Lapidus teaches DNA in supernant is not required to be further isolated by techniques such as sequence-specific capture prior to performing every type of screening assay (see lines 54-61 of column 7, in particular). Further isolation techniques, such as sequence-specific capture, would not be performed to screen for cancer comprising detecting the amount of DNA "greater than about 200 bp" in body excretion, such as a stool sample (see Claim 1 of Lapidus and 47-56 of column 7) or to detect the amount of "amplifiable DNA" prior to further testing (as illustrated in Figure 1). While Lapidus teaches other methods that require further isolation, such as methods requiring detecting particular mutations on captured DNA, this rejection is not based on such methods.

In regards to the indication that Lapidus' teaching of "greather than about 200 bp" does not include 200 bp, the examiner disagrees. Lapidus' methods of detecting "amplifiable DNA" and/or DNA "greater than about 200 bp" includes methods that amplify fragments of 200 bp (or less than 200 bp, in the case of "amplifiable DNA").

In regards to the argument that the cited references do not teach quantifying patient DNA in a stool sample by measuring an amount of nucleic acid fragments amplified from heterogenous DNA isolated from supernant from a centrifuged sample comprising stool sample and buffer, wherein said heterogeneous DNA comprises human DNA that has not been specifically isolated from other DNA in the supernant, Lapidus teaches DNA in supernant is not required to be further isolated by techniques such as sequence-specific capture prior to performing every type of screening assay (see lines 54-61 of column 7, in particular). Further isolation techniques, such as sequence-specific capture, would not be performed to screen for cancer comprising detecting the amount of DNA "greater than about 200 bp" in body excretion, such as a stool sample (see Claim 1 of Lapidus and 47-56 of column 7) or to detect the amount of "amplifiable DNA" prior to further testing (as illustrated in Figure 1). While Lapidus teaches other methods that require further isolation, such as methods requiring detecting particular mutations on captured DNA, this rejection is not based on such methods. Further, Lapidus teaches quantifying patient DNA in a stool sample by measuring an amount of nucleic acid fragments amplified from heterogenous DNA isolated from supernant from a centrifuged sample comprising stool sample and buffer, wherein said heterogeneous DNA comprises human DNA that has not been specifically isolated from other DNA in the supernant (see "amplifiable DNA" of Figure 1 and lines 44-55 of column 4, lines 36-44 of column 5, lines 47-56 of column 7, and claims 1, 6, and 7, in particular).

In regards to the argument that motivation for combining the cited references has not been provided, one of ordinary skill in the art at the time the invention was made would have been motivated to perform the methods of Lapidus et al by describing the amounts of amplifiable DNA and DNA greater than about 200 bp in terms of genomic equivalents because describing amounts of DNA in terms of genomic equivalents effectively normalizes data between multiple samples and assays. Further, one would have been motivated to perform said methods by detecting 200 bp fragments because Lapidus et al teaches a high amount of amplifiable genomic DNA greater than about 200 bp in a stool sample, as compared to a healthy individual, is indicative of a need for further screening and predictive of colorectal cancer because patients with adenoma in the colon slough more cells than healthy individuals. Further,one would have been motivated to perform said methods by detecting fragments less than 200 bp because Lapidus et al teaches a high amount of amplifiable genomic DNA (which includes amplified fragments less than 200 bp; see Figure 1), as compared to a healthy individual, is indicative of a need for further screening of colorectal cancer because patients with adenoma in the colon slough more cells than healthy individuals.